```
     chemotherapeutic agent.  .  .
IT   168682-53-9P   286942-97-0P
     RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
     (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
     (Uses)
        (pharmaceutical compns. containing glutathione analogs)


=> file pctfull
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    11.31      61.97

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -0.75      -2.25

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    SEE
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>>> FOR CHANGES IN PCTFULL PLEASE SEE HELP CHANGE
    (last updated April 10, 2006) <<<

>>> NEW PRICES IN PCTFULL AS OF 01 JULY 2006. FOR DETAILS,
    PLEASE SEE HELP COST <<<

=> s TER () (286 or 199)
         64391 TER
          9512 TERS
         69137 TER
                 (TER OR TERS)
         38923 286
         65479 199
L15         15 TER (W) (286 OR 199)

=> s combination or combined
        452833 COMBINATION
        199923 COMBINATIONS
        492208 COMBINATION
                 (COMBINATION OR COMBINATIONS)
        331462 COMBINED
             3 COMBINEDS
        331463 COMBINED
                 (COMBINED OR COMBINEDS)
L16     564675 COMBINATION OR COMBINED

=> s l15 and l16
L17         14 L15 AND L16

=> s l17 not py>2001
        533324 PY>2001
L18          5 L17 NOT PY>2001

=> d ibib 1-5
```

L18 ANSWER 1 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1999037802 PCTFULL ED 20020515
TITLE (ENGLISH): METHODS TO IDENTIFY MYELOSTIMULANTS
TITLE (FRENCH): METHODES D'IDENTIFICATION DE MYELOSTIMULANTS
INVENTOR(S): KAUVAR, Lawrence, M.
PATENT ASSIGNEE(S): TELIK, INC.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9937802	A1	19990729

DESIGNATED STATES
W: AU CA GD IN JP AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
APPLICATION INFO.: WO 1999-US765 A 19990114
PRIORITY INFO.: US 1998-09/010,390 19980121

L18 ANSWER 2 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1997025342 PCTFULL ED 20020514
TITLE (ENGLISH): TETHERED PRODRUGS BY VIRTUE OF COVALENT LINKAGE WITH ANALOGS OF GLUTATHIONE
TITLE (FRENCH): PRECURSEURS DE MEDICAMENTS LIES PAR UNE LIAISON COVALENTE A L'AIDE D'ANALOGUES DE GLUTATHIONE
INVENTOR(S): LYTTLE, Matthew, H.;
KAUVAR, Lawrence, M.
PATENT ASSIGNEE(S): TERRAPIN TECHNOLOGIES, INC.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9725342	A1	19970717

DESIGNATED STATES
W: AU CA JP AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
APPLICATION INFO.: WO 1996-US20042 A 19961220
PRIORITY INFO.: US 1996-8/582,966 19960104

L18 ANSWER 3 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1996040205 PCTFULL ED 20020514
TITLE (ENGLISH): METABOLIC EFFECTS OF CERTAIN GLUTATHIONE ANALOGS
TITLE (FRENCH): EFFETS METABOLIQUES DE CERTAINS ANALOGUES DE GLUTATHIONE
INVENTOR(S): KAUVAR, Lawrence, M.;
LYTTLE, Matthew, H.;
MORGAN, Amy, S.;
BORCH, Richard, F.
PATENT ASSIGNEE(S): TERRAPIN TECHNOLOGIES, INC.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9640205	A1	19961219

DESIGNATED STATES
W: AL AM AU BB BG BR CA CN CZ EE GE HU IL IS JP KG KP KR LK LR LT LV MD MG MK MN MX NO NZ PL RO SG SI SK TR TT UA UZ VN KE LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
APPLICATION INFO.: WO 1996-US9057 A 19960605
PRIORITY INFO.: US 1995-8/482,645 19950607
US 1996-8/636,516 19960419

L18 ANSWER 4 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1995009866 PCTFULL ED 20020514
TITLE (ENGLISH): GLUTATHIONE S-TRANSFERASE-ACTIVATED COMPOUNDS
TITLE (FRENCH): COMPOSES ACTIVES PAR LA GLUTATHIONE S-TRANSFERASE
INVENTOR(S): KAUVAR, Lawrence, M.;
LYTTLE, Matthew, H.;
SATYAM, Apparao
PATENT ASSIGNEE(S): TERRAPIN TECHNOLOGIES, INC.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9509866	A1	19950413

DESIGNATED STATES
W: AU CA JP AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
APPLICATION INFO.: WO 1994-US11109 A 19940930
PRIORITY INFO.: US 1993-8/130,736 19931001
US 1994-8/309,005 19940919

L18 ANSWER 5 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1995009865 PCTFULL ED 20020514
TITLE (ENGLISH): GLUTATHIONE S-TRANSFERASE-ACTIVATED COMPOUNDS
TITLE (FRENCH): COMPOSES ACTIVES PAR LA GLUTATHIONE S-TRANSFERASE
INVENTOR(S): KAUVAR, Lawrence, M.;
LYTTLE, Matthew, H.;
SATYAM, Apparao
PATENT ASSIGNEE(S): TERRAPIN TECHNOLOGIES, INC.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9509865	A1	19950413

DESIGNATED STATES
W: AU CA JP AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
APPLICATION INFO.: WO 1994-US10796 A 19940923
PRIORITY INFO.: US 1993-8/130,736 19931001
US 1994-8/130,736 19940919

=> d kwic 2-5

L18 ANSWER 2 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD However, TER 117 does not. A prodrug constructed from TER 117 as described in the above-referenced PCT application, TER 286, has the desired isoenzyme specificity for cells having GST complements high in the P1-1 isoform; however, this form of the prodrug would. . .
. . .
or acid at a temperature of from about OOC to about 1000C, preferably at room temperELture either in water alone or in combination with an inert water-miscible organic solvent such as methanol, ethanol or dioxane.
. . .
in the PCT application, TER 231 is especially susceptible to cleavage by GST Mla-la; TER 303 is especially susceptible to cleavage by Al-1; TER 286 is particularly susceptible to cleavage by P1-1 and Al-1, while TER 296 is

selectively cleaved by P1 Thus, in treating a tumor having elevated levels of P1 use of a compound of formula (1) having the tripeptide contained in TER 296 or TER 286 would be preferred. The relevant isoenzyme, GST
P1-1 is elevated in more than 75% of human tumor specimens from breast, lung, liver. . .

L18 ANSWER 3 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD . . . toxic effect of TER199 in contrast to its unesterified form on HT4-1 cells, Figure 2 is a graph showing the effect of various combinations of chlorambucil either alone or in combination with ethacrynic acid or TER199.

. . .
in tumor cells. Third, the compounds of formula (1) directly potentiate the effect of chemotherapeutic agents in the destruction of tumor cells. This combination of qualities makes the compounds of the invention useful both as hematopoiesis potentiating agents directly and to ameliorate the negative effects of chemotherapeutic. . .

. . .
CMB, reducing the concentration CMB needed for 50% cell killing by a DMF of 1,08, In contrast the diethyl ester of 7E-C(Bz)-qG (TER 199) at only 12.5 pM enhanced CMB cytotoxicity by a factor.of 1
Preferential expression of GST isoenzyme P1-1 has been reported in a. . .

. . .
5 when TER199 was administered along with the melphalan, the tumor volume mean was approximately 55% of control. For group 4 administered a combination of melphalan and ethacrynic acid, the volumes were approximately 35% of control. Thus, both ethacrynic acid and TER199 potentiate the effects of. . .

. . .
GM-CSFI G-CSFI M-CSFI
Flt3/Flk-2 and Steel factor (stem cell factor/c-kit ligand). Of particular interest was the finding that TER199 enhances colony formation stimulated by combinations of cytokines. Additionally, the enhancing effect is more pronounced in human than in murine bone marrow, These results suggest that TER199 has. . .

. . .
(60)* 65±4 (44)* 67±5 (49)* 50ng)
'Statistically significant
Table 5: Influence of TER199 on colony formation by normal human bone marrow GM-progenitor cells stimulated by combinations of cytokines.

L18 ANSWER 4 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD Properties and Distribution of GST Isoenzymes
The various GST isoenzymes are dimeric proteins formed by binary combinations of monomers encoded by at least fifteen known genes in four gene families, resulting in the theoretical possibility of several dozen different. . .

. . .
availability of a substantial family of isoenzymes which is unevenly distributed as to its members with respect to normal and tumor tissue, combined with differences

between the family members in substrate specificity and inhibitor sensitivity, makes this family an important target for designing therapies for conditions. . .

Figures 3a and 3b are graphs showing the decomposition of TER 286 and TER 322 by various GSTs.

Figure 5 shows the effect of TER 286 on growth of tumors in mice.

Figure 6 shows the effect of 100-200 mg/kg TER 286 on the GM-CFU in bone marrow of mice.

Figure 7 shows the dose-dependence of bone marrow GM-CFU for administration of TER 286.

Modes of Carrying Out the Invention

The compounds of Formula (1) are prodrugs which can be used selectively to target tissues having. . . specificity to the prodrug provided. As shown below, the prodrugs prepared for illustration, TER 230, as a model compound, and TER 231, TER 286, TER 296 and TER 303 as effective prodrugs, are differentially activated by GST enzymes of the A, 7 and a classes. These. . .

T-Glutamyl-a-Amino-o-((2-ethyl-N,N,N,N-tetra(2'-chloro)ethylphosphoramidate)sulfonyl)propionylglycine, (TER 231);
is
T-Glutamyl-a-Amino-o-((2-ethyl-N,N,N,N-tetra(21-chloro)ethylphosphoramidate)sulfonyl)propionyl-(R)-(-)-phenylglycine (TER 286);
T-Glutamyl-a-Amino-fl-((2-ethyl-N,N,N,N-tetra(21-chloro)ethylphosphoramidate)sulfonyl)propionyl-phenylalanine (TER 303);
7-Glutamyl-a-amino-O-(i-phenyl, 2-ethyl-N,N,N,N-tetra(21-chloroethyl)phosphoramidate)sulfonyl)propionyl glycine. (TER 296);
T-Glutamyl-a-amino-fl-(i-phenyl, 2-ethyl-N,N,N,N-tetra(21-chloroethyl)phosphoramidate)sulfonyl)propionyl (R)-(-)-phenylglycine (TER 297);
T-Glutamyl-u-amino-fl(2-ethyl, N,N-bis(2'-chloroethyl)carbamoyl)sulfonyl)propionyl glycine (TER 322) and its diethyl ester (TER 325); and
T-Glutamyl-u-amino-fl-((2-ethyl-(4-benzyloxy(N,.N,N',N' tetrakis(2-chloroethyl)phosphorodiamidate)) carbamido)sulfonyl)propionyl glycine.

. .
base or acid at a temperature of from about OOC to about 1000C, preferably at room temperature either in water alone or in combination with an inert water-miscible organic solvent such as methanol, ethanol or dioxane.

. .
the compounds exemplified below, TER 231 is especially susceptible to cleavage by GST Mla-la; TER 303 is especially susceptible to cleavage by Al-1; TER 286 is particularly susceptible to cleavage by P1-1 and Al-1, while TER 296 is selectively cleaved by P1 Thus, in treating a tumor. . . tumor, they appear to stimulate GM progenitors in bone marrow. There is relatively

little organ toxicity and no evidence of leukocytosis. For TER 286, the relevant isoenzyme, GST P1-1 is elevated in more than 75'i of human tumor specimens from breast, lung, liver and colon.

. . .

synthesis of TER 296 or TER 297, a-amino-fl-sulfhydryl phenylpropionic acid is substituted for the cysteine residue in the analog. For the synthesis of TER 286, phenylglycine is substituted for glycine in the tripeptide as AAc. For synthesis of TER 303, phenyl alanine is substituted for glycine as. . .

. . .

a sep. funnel, and separated. The lower organic layer was saved, and the aqueous layer was extracted with 100 ml of CH2CL2.The combined organic phases were washed with 500 ml saturated brine and dried over Na2SO4. The solution was filtered and reduced to an oil under. . .

. . .

to separate. The lower organic layer was removed and sav ed, and the upper layer was extracted with 100 ml CH2Cl2. The combined CH2C'21ayers were washed six times with 100 ml portions - 25 of saturated NaC11 and dried over Na2SO4- The solution was filtered and. . .

. . .

9:1. The reaction was quenched with dropwise addition of 100 ml water, and extracted twice with 250 ml portions of EtOAc. The combined organic extracts were washed twice with 100 ml portions of brine and dried over Na2SO4. This was filtered and evaporated to 8.3. . .

. . .

stirred overnight. The mixture was poured into 35 ml of water and extracted with two 50 ml portions of toluene, and the combined organic phases were dried over Na2SO4 and concentrated to a viscous oil. TLC (9:1 EtOAc:MeOH) showed one spot, rf 0 UV active.. . .

T-Glutamyl-u-Amino-o-((2-ethyl,-N,N,N,N-tetra(21-chloro). ethylphosphoramidate)sulfonyl)propionyl-(R)-(-)-phenylglycine (TER 286);
T-Glutamyl-u-Amino-o-((2-ethyl-N,N,N,N-tetra(2'-chloro)ethylphosphoramidate)sulfonyl)propionyl-phenylalanine (TER 303);
T-Glutamyl-u-Amino-O-(1-phenyl, (2-ethyl-N,N,N,N-tetra(2-chloro)ethylphosphoramidate)sulfonyl) propionyl glycine (TER 296);
T-Glutamyl-u-Amino (1-phenyl, (2-ethyl-N,N,N,N-tetra(21-chloro)ethylphosphoramidate)sulfonyl) propionyl (R)-(-)-phenylglycine (TER 297).

Further details with respect to TER 286 are as follows.

TER 286 was similarly tested with the results shown in Figure 3a. Both Pl-l and Al-l accelerate the cleavage of TER 286 roughly six times faster than background; there is negligible acceleration of cleavage with Mla-la.

. . .

prodrug selected, specificity can be obtained for any of the three human GSTs tested. Thus, TER 29G is selectively cleaved by Pi-1; TER 286 is selectively cleaved by PI-1 and Al-1; TER 303 is

selectively cleaved by A1-1; and TER 231 by Mla-1a.

. . .

when
MCF-7 tumor cells transfected by P1-1 were compared to cells transfected only with the control vector. As shown in Figure 4a, when TER 286 is employed, cells containing high P1-1 enzyme
levels are sensitized 4-fold to the prodrug compared to controls; Figure 4b shows a 2-fold. . .

. . .

were obtained for MCF-7 cells which
are sensitive to CTX as compared to CTX-resistant forms. The CTX-resistant cells were more sensitive to TER 286 by a factor
of 1.8 as compared to cells sensitive to CTX in a standard clonogenic assay.

In Figure 5, the squares represent controls; circles represent 300 mg/kg of TER 286; triangles represent 400 mg/kg of the same
drug. The points shown are the mean + SEM of 5-7 mice per group.

Examiple 6
Effect of Prodrug on Bone Marrow
In the assay, B6D2F1 mice were treated with various doses of TER 286 intraperitoneally either as a single injection
or as five daily injections. Femoral bone marrows were harvested 24 hours later and assayed for. . . results are shown in Figure 6. Increases up to 1800i of
controls for GM-CFU were obtained with administration of 100-200 mg/kg of TER 286; the values shown are the mean plus SD of 2-3
experiments.

Further, as shown in Figure 7, the optimum dosage range appears to be in this region of 100-200 mg/kg for TER 286.

L18 ANSWER 5 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD Properties and Distribution of GST Isoenzymes
The various GST isoenzymes are dimeric proteins formed by binary combinations of monomers encoded by at least fifteen known genes in four gene families, resulting in the theoretical possibility of several dozen different. . .

. . .

availability of a substantial family of
isoenzymes which is unevenly distributed as to its members with respect to normal and tumor tissue, combined with differences between the family members in substrate specificity and inhibitor sensitivity, makes this family an important target for designing therapies for conditions. . .

. . .

2 is a graph showing the decomposition of TER 231 by various GSTs,
Figure 3 is a graph showing the decomposition of TER 286 by various GSTs.

. . .

for various chemotherapeutic
agents with respect to cells having high or low levels of GST P1
Figure 5 shows the effect of TER 286 on growth of tumors in mice.

Figure 6 shows the effect of 100-200 mg/kg TER 286
on
the GM-CFU in bone marrow of mice.

Figure 7 shows the dose-dependence of bone marrow GM-
CFU for administration of TER 286.

Modes of Carrying Out the Inventio
The compounds of Formula (1) are prodrugs which can be
used selectively to target tissues having. . . specificity to the
prodrug
provided. As shown below, the prodrugs prepared for
illustration, TER 230, as a model compound, and TER 231, TER
286, TER 296 and TER 303 as effective prodrugs, are
differentially activated by GST enzymes of the A, w and a
classes. These. . .

T-Glutamyl-a-Amino-fl-((2-ethyl-N,N,N,N-tetra(21-
chloro)ethylphosphoramidate)sulfonyl)propionylglycine, (TER 231)1
7-Glutamyl-a-Amino-O-((2-ethyl-N,N,N,N-tetra(21-
chloro)ethylphosphoramidate)sulfonyl)propionyl-(R)-(-)-
phenylglycine (TER 286);
- 13 -
oy-Glutamyl-oi-Amino-O-((2-ethyl-N,N,N,N-tetra(21-
chloro)ethylphosphoramidate)sulfonyl)propionyl-phenylalanine
(TER 303);
T-Glutamyl-a-Amino-fl-(I-phenyl, 2-ethyl-N,N,N,N-
tetra(21-chloro)ethylphosphoramidate)sulfonyl)propionyl glycine
(TER 296);
7-Glutamyl-u-Amino-fl-(1-phenyl, 2-ethyl-N,N,N,N-
tetra(2i-chloro)ethylphosphoramidate)sulfonyl)propionyl (R)-(-)-
phenylglycine (TER 297).

. .
base or
acid at a temperature of from about OOC to about 1000C,
preferably at room temperature either in water alone or in
combination with an inert water-miscible organic solvent such
as
methanol, ethanol or dioxane.

. .
exemplified below, TER 231 is especially susceptible
5 to cleavage by GST Mla-la; TER 303 is especially susceptible to
cleavage by Al-1; TER 286 is particularly
susceptible to
cleavage by P1-1 and Al-1, while TER 296 is selectively cleaved
by PI Thus, in treating a tumor. . . tumor, they appear to
stimulate GM progenitors in bone marrow, There is relatively
little organ toxicity and no evidence of leukocytosis, For TER
286, the relevant isoenzyme, GST PI-1 is elevated in more than
75% of human tumor specimens from breast, lung, liver and colon.

. .
for synthesis of TER 296 or TER
297, a-amino-o-sulfhydryl-o-phenylpropionic acid is substituted
for the cysteine residue in the analog. For the synthesis of
TER 286, phenylglycine is substituted for glycine in
the
tripeptide as AAC. For synthesis of TER 303, phenyl alanine is
substituted for glycine as. . .

. .
sep. funnel,
and separated. The lower organic layer was saved, and the
aqueous layer was extracted with 100 ml of CH2CL2. The combined
organic phases were washed with 500 ml saturated brine and dried
over Na2SO4. The solution was filtered and reduced to an oil

under. . .
. . .
to separate. The lower organic layer was removed and
35 saved, and the upper layer was extracted with 100 ml CH2C12. The
combined CH2C12 layers were washed six times with 100 ml
portions
- 23
of saturated NaC1, and dried over Na2SO4- The solution was
filtered. . .
. . .
9:1. The reaction was
quenched with dropwise addition of 100 ml water, and extracted
twice with 250 ml portions of EtOAc. The combined organic
extracts were washed twice with 100 ml portions of brine and
dried over Na2SO4. This was filtered and evaporated to 8.3. . .
. . .
stirred overnight. The mixture was poured into
35 ml of water and extracted with two 50 ml portions of toluene,
and the combined organic phases were dried over Na2SO4 and
concentrated to a viscous oil. TLC (9:1 EtOAc:MeOH) showed one
spot, rf 0,7, UV active.. . .

7-Glutamyl-u-Amino-g-((2-ethyl-N,N,N,N-tetra(21-
chloro) ethylphosphoramidate)sulfonyl)propionyl-(R)-(-)-
phenylglycine (TER 286);
7-Glutamyl-a-Amino-fl-((2-ethyl-N,N,N,N-tetra(21-
chloro)ethylphosphoramidate)sulfonyl)propionyl-phenylalanine
(TER 303);
7-Glutamyl-a-Amino (1-phenyl, (2-ethyl-N,N,N,N-
tetra(21-chloro)ethylphosphoramidate)sulfonyl) propionyl glycine
(TER 296);
7-Glutamyl-a-Amino-fl-(I-phenyl, (2-ethyl-N,N,N,N-
tetra(21-chloro)ethylphosphoramidate)sulfonyl) propionyl (R)-(-
)-phenylglycine (TER 297).

Further details with respect to TER 286 may be found
in Lyttle, M.H. et al. J Med Chem (1994) 37:1501-1507; Lyttle,
M. et al, J Med Chem (1994) 34:189. . .

TER 286 was similarly tested with the results shown
in
Figure 3. Both PI-1 and Al-1 accelerate the cleavage of TER
286
roughly six times faster than background; there is negligible
acceleration of cleavage with Mla-la.
. . .
when
MCF-7 tumor cells transfected by PI-1 were compared to cells
transfected only with the control vector. As shown in Figure
4a, when TER 286 is employed, cells containing high
P1-1 enzyme
levels are sensitized 4-fLold to the prodrug compared to
controls; Figure 4b shows a 2-fold. . .
. . .
obtained for MCF-7 cells which
are sensitive to CTX as compared to CTX-resistant forms. The
25 CTX-resistant cells were more sensitive to TER 286
by a factor
of 1,8 as compared to cells sensitive to CTX in a standard
clonogenic assay.

- 33 -
In Figure 5, the squares represent controls; circles represent
300 mg/kg of-TER 286; triangles represent 400 mg/kg
of the same

drug. The points shown are the mean ± SEM of 5-7 mice per group.

Example 6
Effect of Prodrug on Bone Marrow
In the assay, B6D2F. mice were treated with various doses of TER 286 intraperitoneally either as a single injection
or as five daily injections. Femoral bone marrows were harvested 24 hours later and assayed for. . . results are shown in Figure 6, Increases up to 18016 of
controls for GM-CPU were obtained with administration of 100-200 mg/kg of TER 286; the values shown are the mean plus SD of 2-3
experiments.

Further, as shown in Figure 7, the optimum dosage range appears to be in this region of 100-200 mg/kg for TER 286.

```
=> s cancer? or tumor? or neoplas?
         80405 CANCER?
         67062 TUMOR?
         23301 NEOPLAS?
L19     100034 CANCER? OR TUMOR? OR NEOPLAS?

=> s l19/clm
         23115 CANCER?/CLM
         15601 TUMOR?/CLM
          3791 NEOPLAS?/CLM
L20      32848 (CANCER?/CLM OR TUMOR?/CLM OR NEOPLAS?/CLM)

=> s l20 and l18
L21          2 L20 AND L18

=> d ibib 1-2

L21    ANSWER 1 OF 2     PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:       1999037802 PCTFULL  ED 20020515
TITLE (ENGLISH):        METHODS TO IDENTIFY MYELOSTIMULANTS
TITLE (FRENCH):         METHODES D'IDENTIFICATION DE MYELOSTIMULANTS
INVENTOR(S):            KAUVAR, Lawrence, M.
PATENT ASSIGNEE(S):     TELIK, INC.
LANGUAGE OF PUBL.:      English
DOCUMENT TYPE:          Patent
PATENT INFORMATION:
                        NUMBER             KIND     DATE
                        ---------------------------------
                        WO 9937802           A1 19990729
DESIGNATED STATES
       W:               AU CA GD IN JP AT BE CH CY DE DK ES FI FR GB GR IE IT
                        LU MC NL PT SE
APPLICATION INFO.:      WO 1999-US765        A  19990114
PRIORITY INFO.:         US 1998-09/010,390      19980121

L21    ANSWER 2 OF 2     PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:       1995009865 PCTFULL  ED 20020514
TITLE (ENGLISH):        GLUTATHIONE S-TRANSFERASE-ACTIVATED COMPOUNDS
TITLE (FRENCH):         COMPOSES ACTIVES PAR LA GLUTATHIONE S-TRANSFERASE
INVENTOR(S):            KAUVAR, Lawrence, M.;
                        LYTTLE, Matthew, H.;
                        SATYAM, Apparao
PATENT ASSIGNEE(S):     TERRAPIN TECHNOLOGIES, INC.
LANGUAGE OF PUBL.:      English
```

DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9509865	A1	19950413

DESIGNATED STATES
W: AU CA JP AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
APPLICATION INFO.: WO 1994-US10796 A 19940923
PRIORITY INFO.: US 1993-8/130,736 19931001
US 1994-8/130,736 19940919

=> s l19 and 18
'RN' IS NOT A VALID FIELD CODE
452833 COMBINATION
199923 COMBINATIONS
492208 COMBINATION
(COMBINATION OR COMBINATIONS)
0 439943-59-6/RN
429338 PY>2002
L22 0 L19 AND L8

=> s l19 and l18
L23 5 L19 AND L18

=> d kwic 3

L23 ANSWER 3 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD . . . effects
can be neutropenia, thrombocytopenia and immune suppression generally. These side effects are not only unpleasant, but they also restrict the efficacy of cancer therapy and place the subject at serious risk of infection and uncontrolled bleeding.

Disclosure of the Invention
The invention provides compounds which are useful in modulating hematopoiesis generally and as aids to chemotherapeutic treatment of tumors by virtue of their ability to exert a protective effect on the hematopoietic system with respect to toxic agents which are otherwise useful. . .
. . .
cell populations in the course of bone marrow transplantation. The invention is further directed to the use of compounds of the invention as tumor-specific chemo- or radiosensitizers, thus potentiating the effect of treatment, and as generalized chemoprotectants,
The invention also includes pharmaceutical compositions containing the compounds of the. . .

Brief Description of the Drawings
Figure la shows the effect of TER199 on the survival of tumor cells treated with various concentrations of chlorambucil.
. . .
toxic effect of TER199 in contrast to its unesterified form on HT4-1 cells,
Figure 2 is a graph showing the effect of various combinations of chlorambucil either alone or in combination with ethacrynic acid or TER199.
. . .

chemotherapeutic agents, Second,
they usually inhibit at least one class of the GST isoenzymes, including the n subclass, which is particularly prevalent in tumor cells. Third, the compounds of formula (1) directly potentiate the effect of chemotherapeutic agents in the destruction of tumor cells. This combination of qualities makes the compounds of the invention useful both as hematopoiesis potentiating agents directly and to ameliorate the negative effects of chemotherapeutic. . .
. .

Example 1
Use of the Compounds of the Invention in Potentiation of Cytotoxic Agents in Human Cells
This example describes: 1) potentiation in human tumor cells of a cytotoxic agent currently used in cancer
chemotherapy by GST inhibitors, including compounds of the present invention, as well as 2) enhanced intracellular efficacy of esterified forms of these compounds,
HT-29 (human colon adenocarcinoma) cells were obtained from Dr, Roberto Ceriani (Cancer Research Fund of Contra Costa County, Walnut Creek, CA) and were used it log phase of growth unless otherwise specified.

The results in Tables 1-3 show that several GSH analogs found to be inhibitors of GSH also potentiate killing of human tumor cells in culture by CMB which is a substrate for various GSTs. Results of potentiation tests with several GST inhibitors in HT29. . .
. .
CMB, reducing the
concentration CMB needed for 50% cell killing by a DMF of 1,08, In contrast the diethyl ester of 7E-C(Bz)-qG (TER 199) at only 12.5 pM enhanced CMB cytotoxicity by a factor.of 1
Preferential expression of GST isoenzyme P1-1 has been reported in a range of human tumors. In the present study the efficacy of CMB potentiation of the several GST inhibitors tested correlated directly with their
- 18 -
potencies as. . .

Example 2
Potentiation of Melphalan Toxicity in vivo
Male scid mice were subcutaneously implanted with HT4-1 tumors from donor mice. HT4-1 is a subclone of HT-29, a human colon cancer. When tumors reached approximately 100 MM3, the mice were randomized into six treatment groups and treated for seven days as follows.

The mice were monitored for weight changes and tumor volumes were determined by measurement with calipers.

The tumor growth was monitored until the average tumor size reached 1500 MM3 for all groups except melphalan with ethacrynic acid. This group failed to reach this volume even after 72 days.

The results were computed in terms of the tumor volume in the drug treated mice as a percentage of control tumor volume (i.e., in the group administered vehicle alone). In group 11 administered melphalan alone, the tumors were approximately 75% of the volume of

controls. In group 5 when TER199 was administered along with the melphalan, the tumor volume mean was approximately 55% of control. For group 4 administered a combination of melphalan and ethacrynic acid, the volumes were approximately 35% of control. Thus, both ethacrynic acid and TER199 potentiate the effects of melphalan, (The volume measurements were taken at the time control tumors reached 1500 nun3

Example 3

Metabolic Effects of the Invention Compounds

The metabolic effects related to toxicity of the compounds of the invention on. . .

. . .

PG intraperitoneally. Femoral bone marrows were harvested 24 hours later and assayed for GM-CFU by the method of East, C.J. et. al. Cancer Chemother Pharmacol (1992) 31:123 An increase in the number of colonies in a dose-dependent manner up to a dosage of 90 mg/kg. . .

. . .

GM-CSFI G-CSFI M-CSFI

Flt3/Flk-2 and Steel factor (stem cell factor/c-kit ligand). Of particular interest was the finding that TER199 enhances colony formation stimulated by combinations of cytokines. Additionally, the enhancing effect is more pronounced in human than in murine bone marrow, These results suggest that TER199 has. . .

. . .

(60)* 65±4 (44)* 67±5 (49)*

50ng)

'Statistically significant

Table 5: Influence of TER199 on colony formation by normal human bone marrow GM-progenitor cells stimulated by combinations of cytokines.

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E4            1     TER 200/CN
E5            1     TER 206/CN
E6            1     TER 211/CN
E7            1     TER 230/CN
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E9            1     TER 286/CN
E10           1     TER 317/CN
E11           1     TER 322/CN
E12           1     TER 324/CN
E13           1     TER 338/CN
E14           1     TER 3938/CN
E15           1     TER 838/CN
E16           1     TER 838, POLYMER WITH TEDIMON 316/CN
E17           1     TER 930180/CN
E18           1     TER BINDING PROTEIN (PLASMID RTS1 GENE ORF91)/CN
E19           1     TER HELL 5603/CN
E20           1     TER HELL 6805/CN
E21           5     TER(5,6)FULLERENE-C50-D5H(6)/CN
E22           3     TER(5,6)FULLERENE-C50-D5H(6), DOCOSAHYDRO-/CN
E23           2     TER(5,6)FULLERENE-C50-D5H(6), OCTADECAHYDRO-/CN
E24           1     TER-1H-INDOLE, 2,2',2'',3,3',3''-HEXAPHENYL-/CN
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L1            1 "TER 199"/CN

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RN   168682-53-9  REGISTRY
CN   Glycine, L-γ-glutamyl-S-(phenylmethyl)-L-cysteinyl-2-phenyl-,
     diethyl ester, (2R)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Glycine, N-[N-L-γ-glutamyl-S-(phenylmethyl)-L-cysteinyl]-D-2-phenyl-
     , diethyl ester
OTHER NAMES:
CN   Ter 199
CN   Terrapin 199
CN   TLK 199
FS   STEREOSEARCH
MF   C27 H35 N3 O6 S
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Absolute stereochemistry.

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